Synthesis and Characterization of Pseudotetrahedral N_2O and N_2S Zinc(II) Complexes of Two Heteroscorpionate Ligands: Models for the Binding Sites of Several Zinc Metalloproteins

Brian S. Hammes and Carl J. Carrano*

Department of Chemistry, Southwest Texas State University, San Marcos, Texas 78666

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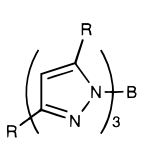
Nine new pseudotetrahedral Zn(II) complexes of the heteroscorpionate ligands (3-*tert*-butyl-2-hydroxy(or thio)-5-methylphenyl)bis(3,5-dimethylpyrazolyl)methane, L1OH or L2SH, have been prepared and characterized (in most cases crystallographically). Complexes isolated include [(L1O)ZnCl], [(L1O)ZnI], [(L1OH)ZnI_2], [(L1O)-$ZnCH_3$], [(L1O)ZnOAc], [(L1O)ZnSPh], [(L1O)ZnSBz], [(L2S)$ZnCH_3$], [(L2S)ZnSPh], and [$(L2S)_2$Zn]. In conjunction with the widely studied tris(pyrazolyl)borates this new series of heteroscorpionates provides a set of isolobal and isoelectronic ligands differing in donor set, i.e. N_3, N_2O, and N_2S. Preliminary reactivity studies with HX species, MeI, or trimethyl phosphate suggest differences between the three sets of ligands.

Introduction

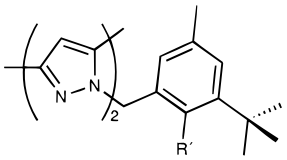
Zinc-containing proteins constitute the largest group of metalloproteins. While the zinc in these proteins has very divergent functions, including both structural and catalytic roles, the nature of its binding site in these proteins is surprisingly similar.[1] Thus the structure of the Zn site in most proteins can usually be described as pseudotetrahedral with N, O, or S donor atoms coming from histidine, tyrosine, aspartic or glutamic acids, cysteine, and/or water. Given the similarities in the overall structures, it is particularly important to understand how the [$N_xO_yS_z$] donor set modulates the reactivity of the pseudotetrahedral Zn(II) center.

One way to approach this question is in synthesis, structural characterization, and reactivity studies of small synthetic analogues to these Zn metalloenzymes, and extensive efforts have been undertaken in this regard. The most successful of these have utilized the tris(pyrazolyl)borates, Tp^R, as a platform, since this ligand provides a facial array of three nitrogen donors from which numerous pseudotetrahedral LZnX complexes have been prepared in elegant work by the Parkin, Vahrenkamp, and Kitajima groups.[2−10] These complexes are excellent structural and reactivity models for certain Zn metalloenzymes such as carbonic anhydrase. However, the Tp group is restricted to providing N_3 donor sets, inappropriate for many of the zinc enzymes, and only recently have efforts by Parkin et. al. been successful in modifying it systematically to produce ligands with mixed N,O,S coordination.[11−14] Vahrenkamp and Fenton have explored other tripodal ligands in an effort to achieve the same goal.[15−18]

Nevertheless, thus far, no single family of easily synthesized complexes with the same coordination geometry, charge, etc., and varying only in the donor set, i.e. N_3, N_2O, and N_2S, has been available for systematic structure and reactivity studies. Formation of N_2S species has been particularly difficult due to the tendency of the sulfur atoms to bridge and produce oligomeric structures.[19,20] In this report we describe a series of Zn complexes with two new heteroscorpionate ligands (L1OH and L2SH) which, along with extensive data already available for the related tris(pyrazolyl)borates, allows us to begin such studies.



Tp^R



R´	Name
OH	L1OH
SH	L2SH

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Experimental Section

All syntheses were carried out in air and the reagents and solvents purchased from commercial sources and used as received unless otherwise noted. Toluene and dichloromethane were distilled under argon over Na/benzophenone and CaH_2, respectively. The syntheses of ligands (3-*tert*-butyl-2-hydroxy-5-methylphenyl)bis(3,5-dimethylpyrazolyl)methane (L1OH) and of (3-*tert*-butyl-5-methyl-2-thiophenyl)bis(3,5-dimethylpyrazolyl)methane (L2SH) followed the reported procedures.[21,22]

[(L1O)ZnCl] (1). A solution of L1OH (0.33 g, 0.89 mmol) in 25 mL of CH_3CN was treated with solid NaOMe (0.048 g, 0.89 mmol) and stirred for 0.5 h. An CH_3CN solution of $ZnCl_2 \cdot 6H_2O$ (0.22 g, 0.89 mmol) was added to the reaction mixture. The resulting solution was stirred for 2 h, concentrated under reduced pressure, and filtered to give a white solid. The white solid was treated with dichloromethane and filtered to remove a small amount of insoluble material (NaCl). The filtrate was concentrated under reduced pressure and crystallized by layering the solution with isopropyl ether (0.27 g, 65%). Anal. Calcd (found) for [(L1O)ZnCl], $C_{22}H_{29}ClN_4OZn$: C, 56.66 (56.33); H, 6.28 (6.32); N, 12.01 (11.86). ^{1}H NMR ($CDCl_3$): δ 7.07 (d, 1 H, $J = 2$ Hz, Ar*H*), 6.90 (s, 1H, $-$C*H*$-$), 6.69 (d, 1 H, $J = 2$ Hz, Ar*H*), 5.94 (s, 1 H, Pz*H*), 2.47 (s, 6 H, Pz$-$CH_3), 2.42 (s, 6 H, Pz$-$CH_3), 2.20 (s, 3 H, Ar$-$CH_3), 1.39 (s, 9 H, $-$C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$): δ 150.53, 140.59, 130.29, 129.06, 120.61, 119.69, 106.71, 73.49, 35.49, 29.43, 20.42, 13.08, 11.59.

[(L1OH)ZnI$_2$] (2). A solution of L1OH (0.22 g, 0.60 mmol) in 25 mL of CH_3CN was treated with a CH_3CN solution of ZnI_2 (0.19 g, 0.60 mmol). The resulting reaction mixture was stirred for 2 h, concentrated under reduced pressure, and filtered to give a white solid. Layering a CH_2Cl_2 solution of [(L1OH)ZnI_2] with isopropyl ether crystallized the complex (0.29 g, 81%). Anal. Calcd (found) for [(L1OH)ZnI_2]$\cdot$$CH_2Cl_2$, $C_{23}H_{32}Cl_2I_2N_4OZn$: C, 35.85 (36.20); H, 4.19 (4.08); N, 7.26 (7.25). FTIR (KBr, cm^{-1}): ν_{OH}(Ar$-$OH) = 3588. ^{1}H NMR ($CDCl_3$): δ 7.73 (s, 1 H, $-$C*H*$-$), 7.17 (d, 1 H, $J = 2$ Hz, Ar*H*), 7.03 (d, 1 H, $J = 2$ Hz, Ar*H*), 6.04 (s, 1 H, Pz*H*), 5.15 (s, 1 H, O*H*), 2.60 (s, 6 H, Pz$-$CH_3), 2.51 (s, 6 H, Pz$-$CH_3), 2.29 (s, 3 H, Ar$-$CH_3), 1.39 (s, 9 H, $-$C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$): δ 154.95, 147.93, 143.89, 133.75, 131.19, 129.54, 127.05, 122.13, 108.22, 64.41, 33.55, 30.55, 21.13, 15.18, 11.66.

[(L1O)ZnI] (3). A solution of L1OH (0.48 g, 1.3 mmol) in 25 mL of CH_3CN was treated with solid NaOMe (0.054 g, 1.3 mmol) and stirred for 0.5 h. A CH_3CN solution of ZnI_2 (0.41 g, 1.3 mmol) was added to the reaction mixture. The resulting solution was stirred for 2 h, concentrated under reduced pressure, and crystallized by layering the CH_2Cl_2 solution with isopropyl ether (0.36 g, 50%). Anal. Calcd (found) for [(L1O)ZnI]$\cdot$$0.35CH_2Cl_2$, $C_{22.35}H_{29.7}Cl_{0.7}IN_4OZn$: C, 45.69 (45.58); H, 5.11 (4.92); N, 9.54 (9.34). ^{1}H NMR ($CDCl_3$): δ 7.07 (d, 1 H, $J = 2$ Hz, Ar*H*), 6.91 (s, 1H, $-$C*H*$-$), 6.69 (d, 1 H, $J = 2$ Hz, Ar*H*), 5.93 (s, 1 H, Pz*H*), 2.48 (s, 6 H, Pz$-$CH_3), 2.47 (s, 6 H, Pz$-$CH_3), 2.20 (s, 3 H, Ar$-$CH_3), 1.39 (s, 9 H, $-$C(CH_3)$_3$). ^{13}C ($CDCl_3$): δ 163.33, 150.80, 142.71, 140.31, 130.17, 128.82, 120.47, 119.65, 107.02, 73.45, 35.51, 29.47, 20.53, 13.97, 11.70.

[(L1O)ZnCH$_3$] (4). A solution of L1OH (2.1 g, 5.7 mmol) in 100 mL of toluene was treated with a toluene solution of $Zn(CH_3)_2$ (0.54 g, 5.7 mmol) under argon. The resulting solution was stirred for 1 h and filtered to yield 2.31 g (91%) of [(L1O)ZnCH_3]. Anal. Calcd (found) for [(L1O)ZnCH_3]$\cdot$$0.25H_2O$, $C_{23}H_{32.5}N_4O_{1.25}Zn$: C, 61.32 (61.38); H, 7.29 (7.27); 12.44 (12.77). ^{1}H NMR ($CDCl_3$): δ 7.02 (d, 1 H, $J = 2$ Hz, Ar*H*), 6.82 (s, 1 H, $-$C*H*$-$), 6.68 (d, 1 H, $J = 2$ Hz, Ar*H*), 5.85 (s, 1 H, Pz*H*), 2.43 (s, 6 H, Pz$-$CH_3), 2.27 (s, 6 H, Pz$-$CH_3), 2.18 (s, 3 H, Ar$-$CH_3), 1.38 (s, 9 H, $-$C(CH_3)$_3$), $-$0.59 (s, 3 H, Zn$-$CH_3). ^{13}C NMR ($CDCl_3$): δ 164.12, 149.29, 142.13, 139.56, 129.66, 128.78, 120.20, 118.62, 106.09, 73.30, 35.33, 29.29, 20.43, 13.06, 11.54, $-$17.03.

[(L1O)ZnOAc] (5). A solution of **4** (0.40 g, 0.90 mmol) in 30 mL of CH_2Cl_2 was treated 1 equiv of HOAc (0.054 g, 0.90 mmol) under argon. The resulting solution was stirred for 1 h and concentrated under reduced pressure. The complex was crystallized by layering a concentrated CH_2Cl_2 solution with diethyl ether (0.39 g, 85%). Anal. Calcd (found) for [(L1O)ZnOAc]$\cdot$$0.75H_2O$, $C_{24}H_{33.5}N_4O_{3.75}Zn$: C, 57.25 (57.61); H, 6.72 (6.61); N, 11.13 (10.77). FTIR (KBr, cm^{-1}): ν_{CO}(OAc$^-$) = 1601, 1393. ^{1}H NMR (CD_2Cl_2): δ 7.00 (d, 1 H, $J = 2$ Hz, Ar*H*), 6.91 (s, 1H, $-$C*H*$-$), 6.71 (d, 1 H, $J = 2$ Hz, Ar*H*), 5.97 (s, 1 H, Pz*H*), 2.46 (s, 6 H, Pz$-$CH_3), 2.31 (s, 6 H, Pz$-$CH_3), 2.17 (s, 3 H, Ar$-$CH_3), 2.14 (s, 3 H, OC(O)CH_3), 1.35 (s, 9 H, $-$C(CH_3)$_3$). ^{13}C NMR (CD_2Cl_2): δ 150.31, 142.02, 141.01, 129.94, 129.00, 120.42, 119.20, 106.59, 73.53, 65.70, 35.34, 29.29, 21.56, 20.18, 15.22, 12.69, 11.57.

[(L1O)ZnSPh] (6). A solution of **4** (0.41 g, 0.91 mmol) in 20 mL of CH_2Cl_2 was treated with a CH_2Cl_2 solution of thiophenol (0.10 g, 0.91 mmol). The resulting solution was stirred for 1 h, dried under reduced pressure, and crystallized by layering an CH_2Cl_2 solution of the complex with isopropyl ether to yield 0.18 g (34%). Anal. Calcd (found) for [(L1O)ZnSPh], $C_{28}H_{34}N_4OSZn$: C, 62.26 (62.11); H, 6.36 (6.23); 10.37 (10.34). ^{1}H NMR ($CDCl_3$): δ 7.69 (d, 2 H, $J = 7$ Hz, SAr*H*), 7.09 (d, 1 H, $J = 2$ Hz, Ar*H*), 7.08 (t, 2 H, $J = 7$ Hz, SAr*H*), 6.97 (t, 1 H, $J = 7$ Hz, SAr*H*), 6.92 (s, 1 H, $-$C*H*$-$), 6.71 (d, 1 H, $J = 2$ Hz, Ar*H*), 5.90 (s, 1 H, Pz*H*), 2.45 (s, 6 H, Pz$-$CH_3), 2.24 (s, 6 H, Pz$-$CH_3), 2.21 (s, 3 H, Ar$-$CH_3), 1.41 (s, 9 H, $-$C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$): δ 150.44, 142.64, 140.63, 140.40, 132.54, 130.24, 129.11, 128.16, 122.59, 120.38, 119.92, 106.67, 73.45, 35.43, 29.40, 20.41, 12.84, 11.61.

[(L1O)ZnSBz] (7). A solution of **4** (0.45 g, 1.1 mmol) in 20 mL of CH_2Cl_2 was treated with a CH_2Cl_2 solution of benzyl mercaptan (0.13 g, 1.1 mmol). The resulting solution was stirred for 15 h and dried under reduced pressure to give [(L1O)ZnSBz] (0.36 g, 60%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 7.50 (d, 2 H, $J = 7$ Hz, SCH_2Ar*H*), 7.23 (t, 2 H, $J = 7$ Hz, SCH_2Ar*H*), 7.12 (t, 1 H, $J = 7$ Hz, SCH_2Ar*H*), 7.10 (d, 1 H, $J = 2$ Hz, Ar*H*), 6.89 (s, 1 H, $-$C*H*$-$), 6.73 (d, 1 H, $J = 2$ Hz, Ar*H*), 5.87 (s, 1 H, Pz*H*), 4.08 (s, 2 H, SCH_2Ar), 2.45 (s, 6 H, Pz$-$CH_3), 2.22 (s, 6 H, Pz$-$CH_3), 2.22 (s, 3 H, Ar$-$CH_3), 1.45 (s, 9 H, $-$C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$): δ 163.20, 150.34, 145.70, 142.32, 140.18, 140.40, 130.12, 129.09, 128.33, 128.13, 125.50, 120.08, 119.97, 107.06, 106.46, 73.43, 35.54, 29.64, 29.57, 20.52, 13.03, 11.70.

[(L2S)ZnCH$_3$] (8). A solution of L2SH (0.78 g, 2.0 mmol) in 50 mL of toluene was treated with a toluene solution of $Zn(CH_3)_2$ (0.19 g, 2.0 mmol) under argon. The resulting solution was stirred for 1 h and filtered to yield 0.39 g (43%) of [(L2S)ZnCH_3]. Anal. Calcd (found) for [(L2S)ZnCH_3]$\cdot$$0.3C_7H_8$, $C_{25.1}H_{34.4}N_4SZn$: C, 61.56 (61.66); H, 7.09 (6.89); N, 11.44 (11.24). ^{1}H NMR (CD_2Cl_2): δ 7.17 (d, 1 H, $J = 2$ Hz, Ar*H*), 7.14 (s, 1H, $-$C*H*$-$), 6.80 (d, 1 H, $J = 2$ Hz, Ar*H*), 6.02 (s, 1 H, Pz*H*), 2.38 (s, 6 H, Pz$-$CH_3), 2.29 (s, 6 H, Pz$-$CH_3), 2.22 (s, 3 H, Ar$-$CH_3), 1.58 (s, 9 H, $-$C(CH_3)$_3$), $-$0.62 (s, 3 H, Zn$-$CH_3). ^{13}C NMR (CD_2Cl_2): δ 153.12, 150.84, 142.24, 135.81, 130.59, 130.46, 129.73, 129.43, 107.53, 75.60, 38.15, 30.49, 20.99, 13.54, 12.15, $-$14.71.

[(L2S)ZnSPh] (9). A solution of **8** (0.11 g, 0.23 mmol) in 20 mL of CH_2Cl_2 was treated with a CH_2Cl_2 solution of thiophenol (0.026 g, 0.23 mmol). The resulting solution was stirred for 1 h, dried under reduced pressure, and crystallized by layering a CH_2Cl_2 solution of [(L2S)ZnSPh] with isopropyl ether to yield 0.063 g (49%) of the complex. Anal. Calcd (found) for [(L2S)ZnSPh]$\cdot$$0.4CH_2Cl_2$, $C_{28.4}H_{34.8}N_4Cl_{0.4}S_2Zn$: C, 57.80 (57.21); H, 5.96 (5.85); 9.49 (9.34). ^{1}H NMR ($CDCl_3$): δ 7.52 (d,2 H, $J = 7$ Hz, SAr*H*), 7.23 (d, 1 H, $J = 2$ Hz, Ar*H*), 7.18 (s, 1 H, $-$C*H*$-$), 7.04 (t, 2 H, $J = 7$ Hz, SAr*H*), 6.93 (t, 1 H, $J = 7$ Hz, SAr*H*), 6.77 (d, 1 H, $J = 2$ Hz, Ar*H*), 5.98 (s, 2 H, Pz*H*), 2.43 (s, 6 H, Pz$-$CH_3), 2.26 (s, 6 H, Pz$-$CH_3), 2.25 (s, 3 H, Ar$-$CH_3), 1.62 (s, 9 H, $-$C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$): δ 153.77, 151.65, 141.91, 141.18, 135.12, 132.35, 130.79, 129.65, 128.04, 122.44, 107.68, 74.99, 37.84, 30.38, 20.88, 13.07, 11.84.

[(L2S)$_2$Zn] (10). The zinc complex **8** (0.10 g, 0.21 mmol) was dissolved in 20 mL of undried CH_2Cl_2. The resulting solution was stirred for 1 h, concentrated under reduced pressure, and crystallized by layering the CH_2Cl_2 solution with isopropyl ether to yield 0.042 g (25%). Anal. Calcd (found) for [(L2S)$_2$Zn], $C_{44}H_{58}N_8S_2Zn$: C, 63.78 (63.68); H, 7.07 (6.88); 13.52 (13.51). ^{1}H NMR ($CDCl_3$): δ 10.28 (s, 1 H, $-$C*H*), 7.67 (d, 1 H, Ar*H*), 7.13 (d, 1 H, Ar*H*), 5.93 (s, 1 H, Pz*H*), 5.61 (s, 1 H, Pz*H*), 2.31 (s, 3 H, Pz$-$CH_3), 2.27 (s, 3 H, Pz$-$CH_3), 2.22 (s, 3 H, Ar$-$CH_3), 1.79 (s, 3 H, Pz$-$CH_3), 1.49 (s, 9 H, $-$C(CH_3)$_3$), 0.68 (s, 3 H, Pz$-$CH_3). ^{13}C NMR ($CDCl_3$): δ 150.64, 148.50, 147.82, 142.47, 140.80, 140.11, 136.78, 131.08, 129.24, 128.59, 108.17, 106.96, 72.43, 37.41, 30.16, 21.66, 14.08, 11.09, 10.84, 10.47.

Table 1. Summary of Crystallographic Data and Parameters for [(L1O)ZnCl] (**1**), [(L1OH)ZnI_2]·CH_2Cl_2 (**2**), [(L1O)$ZnCH_3$] (**4**), [(L1O)ZnOAc]·$(CH_3CH_2)_2O$ (**5**), [(L1O)ZnSPh]·0.5H_2O (**6**), [(L2S)ZnSPh]·0.5CH_2Cl_2 (**8**), and [(L2S)$_2$Zn] (**9**)

	1	**2**	**4**	**5**	**6**	**8**	**9**
molecular formula	$C_{22}H_{29}ClN_4OZn$	$C_{23}H_{32}Cl_2I_2N_4OZn$	$C_{23}H_{32}N_4OZn$	$C_{28}H_{42}N_4O_4Zn$	$C_{28}H_{35}N_4O_{1.5}SZn$	$C_{28.5}H_{35}ClN_4S_2Zn$	$C_{44}H_{58}N_8S_2Zn$
fw	466.31	809.31	445.99	564.14	549.03	598.27	828.47
temp (K)	198(2)	198(2)	198(2)	198(2)	198(2)	198(2)	293(2)
cryst system	monoclinic	Monoclinic	monoclinic	triclinic	triclinic	triclinic	orthorhombic
space group	$P2_1/m$	$P2_1/c$	$P2_1/m$	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$	$P2_12_12_1$
cell constants							
a (Å)	9.412(3)	11.362(2)	9.5569(10)	9.2239(11)	14.5238(8)	13.148(2)	10.996(2)
b (Å)	13.222(4)	14.205(4)	13.139(3)	11.6457(12)	15.217(2)	15.276(2)	14.959(2)
c (Å)	18.928(6)	17.831(3)	18.739(2)	13.485(2)	15.452(2)	15.824(4)	26.801(3)
α (deg)	90	90	90	69.304(9)	76.698(9)	73.609(11)	90
β (deg)	91.34(3)	91.451(11)	91.202(8)	87.755(9)	65.290(9)	85.442(12)	90
γ (deg)	90	90	90	85.424(9)	66.110(6)	71.044(9)	90
Z	4	6	4	2	2	2	4
V (Å^3)	2354.9(14)	2877.0(10)	2352.6(6)	1350.6(3)	2829.1(5)	2883.4(9)	4408.5(13)
abs coeff, μ_{calc} (mm^{-1})	1.175	3.208	1.291	1.137	0.970	1.111	0.692
δ_{calc} (g/cm^3)	1.315	1.779	1.397	1.347	1.289	1.335	1.248
F(000)	976	1504	1016	558	1156	1212	1760
cryst dimens (mm)	0.2 × 0.3 × 0.1	0.7 × 0.7 × 0.7	0.7 × 0.7 × 0.2	0.7 × 0.7 × 0.4	0.4 × 0.4 × 0.2	0.9 × 0.4 × 0.15	0.6 × 0.4 × 0.4
radiation (λ (Å))	Mo Kα (0.710 73)	Mo Kα (0.710 73)	Mo Kα (0.710 73)	Mo Kα (0.710 73)	Mo Kα (0.710 73)	Mo Kα (0.710 73)	Mo Kα (0.710 73)
h,k,l ranges collcd	0 → 8, 0 → 14, −20 → 20	0 → 12, 0 → 14, −19 → 19	0 → 10, −12 → 0, −20 → 20	−8 → 8, −11 → 11, −14 → 14	−12 → 12, −14 → 16, −15 → 16	−14 → 0, −14 → 14, −17 → 16	−11 → 0, −15 → 0, −28 → 0
θ range (deg)	1.88−22.50	1.83−22.50	1.89−22.50	1.87−22.50	1.78−22.50	2.03−22.50	2.00−22.49
no. of reflcns collcd	3181	4063	3237	3498	7159	7464	2851
no. of unique reflcns	2957	3523	3040	3240	6812	7101	2819
no. of params	301	298	301	332	646	677	497
data/param ratio	9.81	11.82	10.06	9.75	10.52	10.49	5.67
refinement method	full-matrix least squares on F^2	full-matrix least squares of F^2	full-matrix least squares of F^2	full-matrix least squares of F^2	full-matrix least squares of F^2	full-matrix least squares of F^2	full-matrix least squares of F^2
$R(F)^a$	0.0701	0.0436	0.0542	0.0523	0.0676	0.0433	0.0419
$R_w(F^2)^b$	0.1439	0.1131	0.1459	0.1350	0.1848	0.1083	0.1053
GOFw^c	1.041	1.130	1.075	0.981	1.064	0.973	1.041
largest diff peak and hole (e/Å^3)	0.467, −0.398	1.006, −1.493	0.746, −1.154	0.465, −0.710	1.299, −1.368	0.899, −0.579	0.409, −0.650

[a] $R = [\sum|\Delta F|/\sum|F_o|]$. [b] $R_w = [\sum w(\Delta F)^2/\sum wF_o^2]$. [c] Goodness of fit on F^2.

Physical Methods. Elemental analyses were performed on all compounds by Desert Analytics, Inc., Tucson, AZ, or Quantitative Technologies, Inc., Whitehouse, NJ. All samples were dried in vacuo prior to analysis. The presence of solvates was corroborated by FTIR, ^{1}H NMR, or X-ray crystallography. ^{1}H and ^{13}C NMR spectra were collected on a Varian UNITY INOVA 400 MHz NMR spectrometer. Chemical shifts are reported in ppm relative to an internal standard of TMS. The ^{13}C quaternary carbon peaks that are not observed are a result of either poor solubility and/or overlapping signals. IR spectra were recorded from KBr disks on a Perkin-Elmer 1600 Series FTIR spectrometer and are reported in wavenumbers.

Crystallographic Structure Determination. Crystal, data collection, and refinement parameters for [(L1O)ZnCl] (**1**), [(L1OH)ZnI_2] (**2**), [(L1O)$ZnCH_3$] (**4**), [(L1O)ZnOAc] (**5**), [(L1O)ZnSPh] (**6**), [(L2S)ZnSPh] (**9**), and [(L2S)$_2$Zn] (**10**) are given in Table 1. Crystals of all complexes were sealed in thin-walled quartz capillaries, and data collection was initiated at 198 K except for **10**, the data for which were obtained at room temperature. The systematic absences in the diffraction data are consistent with the space groups $P\bar{1}$ for [(L1O)ZnOAc]·$(CH_3CH_2)_2O$, [(L1O)ZnSPh]·0.5H_2O, and [(L2S)ZnSPh]·0.5CH_2Cl_2, $P2_1/m$ for [(L1O)ZnCl] and [(L1O)$ZnCH_3$], $P2_1/c$ for [(L1OH)ZnI_2]·CH_2Cl_2, and $P2_12_12_1$ for [(L2S)$_2$Zn]. The structures were solved using either direct methods or Patterson techniques, completed by subsequent difference Fourier syntheses, and refined by full-matrix least-squares procedures on F^2. The metal complexes [(L1O)ZnCl] (**1**), [(L1O)$ZnCH_3$] (**4**), [(L1O)ZnSPh] (**6**), and [(L2S)ZnSPh] (**9**) all crystallized with two crystallographically independent, but virtually identical, molecules per unit cell. The metrical parameters quoted in the text refer to only one of the molecules, but structural parameters of both crystallographically independent molecules are available in the Supporting Information. The asymmetric unit of [(L2S)ZnSPh]·0.5CH_2Cl_2 contains half of a molecule of CH_2Cl_2 while [(L1OH)ZnI_2]·CH_2Cl_2 contains a full molecule of this solvent. The asymmetric unit of [(L1O)ZnSPh]·0.5H_2O contains half of a molecule of H_2O, and that of [(L1O)ZnOAc]·$(CH_3CH_2)_2O$ contains a highly disordered lattice diethyl ether. All non-hydrogen atoms were refined with anisotropic displacement coefficients and treated as idealized contributions using a riding model except where noted. All software and sources of the scattering factors are contained in the SHELXTL (5.0) program library (G. Sheldrick, Siemens XRD, Madison WI).

Results

Solid-State Structures of the Complexes. The single-crystal X-ray diffraction studies on [(L1O)ZnCl], [(L1OH)ZnI_2], [(L1O)$ZnCH_3$], [(L1O)ZnOAc], [(L1O)ZnSPh], and [(L2S)ZnSPh] confirm that $(L1O)^-$ or $(L2S)^-$, formed by deprotonation of the phenol oxygen or thiophenol sulfur in L1OH or L2SH, respectively, binds to the zinc in a tridentate fashion. Selected bond distances and angles for these complexes are shown in Tables 2 and 3, and Figures 1−4 contain the thermal ellipsoid diagrams. The molecular structures of [(L1OH)ZnI_2] (**2**) and [(L2S)$_2$Zn] (**10**), however, show different coordination modes of the ligands (Figures 1B and 5), and selected bond lengths and angles for these species are found in Tables 2 and 4, respectively.

Table 2. Selected Bond Distances (Å) and Angles (deg) for [(L1O)ZnCl] (**1**), [(L1OH)ZnI_2] (**2**), [(L1O)$ZnCH_3$] (**4**), and [(L1O)ZnOAc] (**5**)[a]

	1	2	4	5
Zn(1)−N(2)	2.030(8)	2.042(6)	2.077(4)	2.033(4)
Zn(1)−N(2)#1	2.030(8)		2.077(4)	
Zn(1)−N(4)		2.047(6)		2.066(4)
Zn(1)−O(1)	1.901(10)		1.923(5)	1.909(3)
Zn(1)−O(2)				1.945(4)
Zn(1)−O(3)				2.476(5)
Zn(1)−Cl(1)	2.162(5)			
Zn(1)−I(1)		2.5383(10)		
Zn(1)−I(2)		2.5548(10)		
Zn(1)−C(33)			1.952(7)	
N(2)−Zn(1)−N(2)#1	87.7(5)		87.0(2)	
N(2)−Zn(1)−N(4)		92.7		89.33(14)
N(2)−Zn(1)−O(1)	100.3(3)		95.6(2)	99.73(13)
N(2)#1−Zn(1)−O(1)	100.3(3)		95.6(2)	
N(4)−Zn(1)−O(1)				97.10(13)

[a] Numbers in parentheses are estimated standard deviations.

Table 3. Selected Bond Distances (Å) and Angles (deg) for [(L1O)ZnS-Ph] (**6**) and [(L2S)ZnS-Ph] (**8**)[a]

	6	8
Zn(1)−N(2)	2.065(6)	2.030(4)
Zn(1)−N(4)	2.040(2)	2.052(4)
Zn(1)−O(1)	1.921(5)	
Zn(1)−S(1)	2.221(2)	2.246(1)
Zn(1)−S(2)		2.273(1)
N(2)−Zn(1)−N(4)	89.6(2)	91.13(14)
N(2)−Zn(1)−O(1)	93.8(2)	
N(4)−Zn(1)−O(1)	100.2(2)	
S(1)−Zn(1)−O(1)	127.7(2)	
S(1)−Zn(1)−N(2)	121.8(2)	118.91(10)
S(1)−Zn(1)−N(4)	115.5(2)	117.67(10)
S(1)−Zn(1)−S(2)		122.16(5)
S(2)−Zn(1)−N(2)		102.44(10)
S(2)−Zn(1)−N(4)		98.64(10)

[a] Numbers in parentheses are estimated standard deviations.

Complexes Containing (L1O)$^-$. The single-crystal X-ray diffraction study on [(L1OH)ZnI_2] (Figure 1B) confirms the tetrahedral coordination geometry around the zinc ion with two pyrazolyl nitrogen donors of L1OH and two I^- ions coordinated to the zinc ion. The N(2)−Zn(1)−N(4) bond angle in [(L1OH)-ZnI_2] is 92.7(2)°, while the iodide ions occupy the two remaining coordination sites cis to the pyrazole rings with the average N_{pz}−Zn−I bond angle of 111.7(1)°. The phenol oxygen is protonated and not coordinated to the Zn(II) but is rotated away from the metal and oriented in such a way that oxygen O(1) is pointed toward an iodide ion of an adjacent molecule with an O(1)H···I distance of 3.68−3.78 Å.[23]

[(L1O)ZnCl] (Figure 1A), [(L1O)$ZnCH_3$] (Figure 2), and [(L1O)ZnSPh] (Figure 4A) all display a pseudotetrahedral geometry around the metal where the two pyrazolyl nitrogens and one phenolate oxygen donor from $(L1O)^-$ constitute the trigonal face of the tetrahedron. The average N_{pz}−Zn−O_{ph} angle for these complexes are similar, ranging from 95.6(2)° for [(L1O)$ZnCH_3$] to 100.3(3)° for [(L1O)ZnCl]. The N_{pz}−Zn−N_{pz} bond angle ranges from 87.0(2)° for [(L1O)$ZnCH_3$] to 89.6-(2)° for [(L1O)ZnSPh]. Both the N_{pz}−Zn−N_{pz} and average N_{pz}−Zn−O_{ph} bond angles in the complex deviate from the 109.5° angle expected for idealized tetrahedral geometry due to the relatively small bite angle of the ligand. In all cases the seven-membered chelate ring, which contains the phenolate oxygen, supports the larger internal angle. The Cl^- ligand in [(L1O)ZnCl] is positioned perpendicular to the trigonal plane formed by the two pyrazolyl nitrogens and the phenolate oxygen of $(L1O)^-$ which results in an average Zn(1)−Cl(1) bond distance of 2.162(5) Å and average N_{pz}−Zn(1)−Cl(1) and O(1)−Zn(1)−Cl(1) bond angles of 123.2(3) and 116.3(3)°, respectively. In [(L1O)$ZnCH_3$], the Zn(1)−C(33) bond distance of 1.952(7) Å is not unusual and is similar to those reported for other zinc complexes.[24] In [(L1O)ZnSPh] the thiophenol $(S-Ph)^-$ occupies the fourth coordination site on the zinc with a Zn(1)−S(1) bond distance of 2.224(1) Å and average N_{pz}−Zn(1)−S(1) and O_{ph}−Zn(1)−S(1) bond angles of 118.6(1) and 127.2(2)°, respectively.

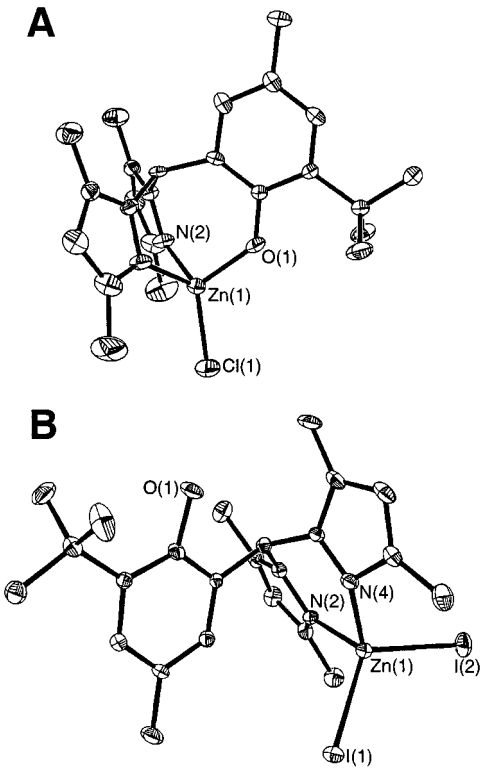

Figure 1. ORTEP diagram with 30% thermal ellipsoids for (a) [(L1O)-ZnCl] and (b) [(L1OH)ZnI_2] showing atomic labeling for the coordination sphere only.

(21) Hammes, B. S.; Carrano, C. J. *Inorg. Chem*. **1999**, *38*, 3562.
(22) Higgs, T.; Carrano, C. J. Manuscript in preparation.
(23) Desiraju, G. D. Crystal Engineering: Design of Organic Solids; Elsevier: New York, 1989.
(24) Looney, A.; Han, R.; Gorrell, I. B.; Cornebise, M.; Yoon, K.; Parkin, G.; Rheingold, A. L. *Organometallics* **1995**, *14*, 274.

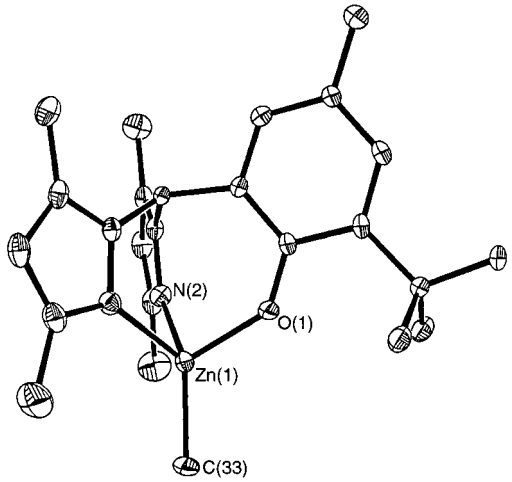

Figure 2. ORTEP diagram with 30% thermal ellipsoids for [(L1O)-$ZnCH_3$] showing atomic labeling for the coordination sphere only.

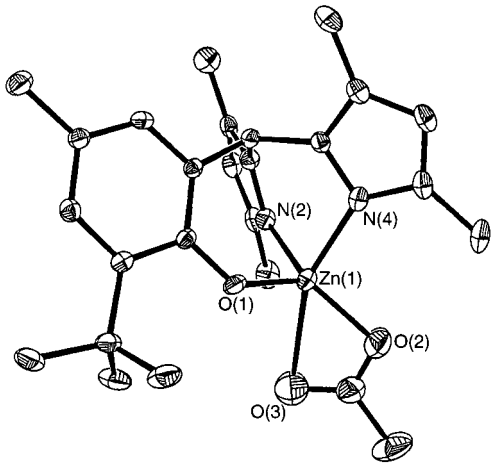

Figure 3. ORTEP diagram with 30% thermal ellipsoids for [(L1O)-ZnOAc] showing atomic labeling for the coordination sphere only.

The molecular structure of [(L1O)ZnOAc] (Figure 3) shows a distorted geometry about the Zn(II) ion with the two pyrazole nitrogen and the phenolate oxygen from the tridentate ligand $(L1O)^-$ coordinated facially to the metal ion. The N(2)−Zn-(1)−N(4) and average N_{pz}−Ni(1)−O(1) bond angle for [(L1O)-ZnOAc] are 89.33(14) and 98.41(10)°, respectively. The acetate is bound neither in a unidentate nor symmetrical bidentate fashion, adopting instead an intermediate coordination mode with Zn(1)−$O_{acetate}$ bond lengths of 1.945(4) and 2.475(5) Å and a Zn(1)−O(2)−C(24) bond angle of 105.1(4)°.[25] The analogous binding of nitrate to the phenyl-substituted tris-(pyrazolyl)borate shows virtually identical metrical parameters. Both nitrate and acetate bind to the more sterically congested *tert*-butyl-substituted derivative in a unidentate fashion with Zn−$O_{acetate}$ bonds of 1.859 and 2.95 Å and a near 109° M−$O_{acetate}$−$C_{acetate}$ angle reported for the latter.[24] These observations suggest that steric interactions play a major role. However electronic factors are also important since the Cu analogue of [(L1O)-ZnOAc] shows symmetrical bidentate acetate coordination with both Cu−O bonds near 2.005(5) Å and a M−O−C angle of 89.2(8)°.[26] Parkin has shown that the mode of nitrate binding

(25) Parkin has discussed the use of the M−O−X angle as a rapid indicator of the denticity of the acetate in such complexes with unidentate binding displaying a 109° M−O−X angle and with a symmetrical bidentate acetate showing an angle of 90°; see: Han, R.; Parkin, G. *J. Am. Chem. Soc.* **1991**, *113*, 9707.

(26) Hammes, B. S.; Carrano, C. J. Unpublished observations.

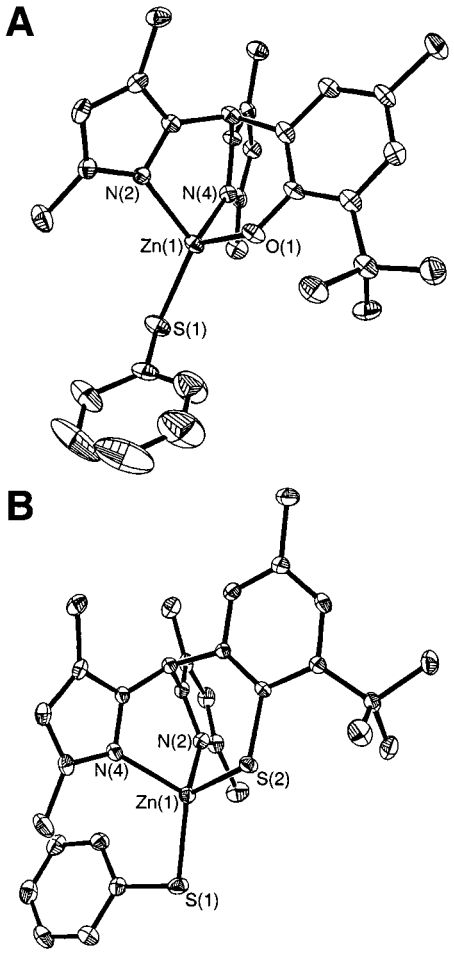

Figure 4. ORTEP diagram with 30% thermal ellipsoids for (a) [(L1O)-ZnSPh] and (b) [(L2S)ZnSPh] showing atomic labeling for the coordination sphere only.

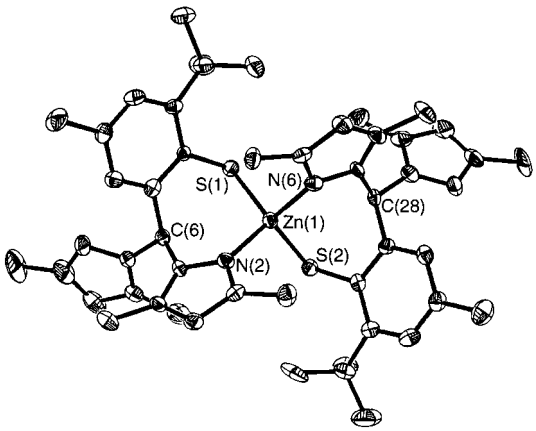

Figure 5. ORTEP diagram with 30% thermal ellipsoids for $[(L2S)_2Zn]$ showing atomic labeling for the coordination sphere only.

to the metal in the *tert*-butyl-substituted tris(pyrazolyl)borate complexes varies as a function of metal from strictly unidentate (Zn) to asymmetric (Co) to symmetrical bidentate (Ni and Cu).[25] This has led to the hypothesis that the binding mode of potentially bidentate ligands such as acetate and nitrate to the Zn reflects the order of reactivity of the purported bicarbonate intermediate in carbonic anhydrase catalyzed hydration of CO_2, i.e. Zn > Co ≫ Cu, Ni.[9] Both mono- and bidentate binding of aspartate and glutamate residues to Zn in the active site of many Zn metalloproteases is known.[1]

Table 4. Selected Bond Distances (Å) and Angles (deg) for $[(L2S)_2Zn]$ (**9**)[a]

Zn(1)−N(2)	2.083(7)	Zn(1)−S(1)	2.286(2)
Zn(1)−N(6)	2.085(6)	Zn(1)−S(2)	2.295(2)
N(2)−Zn(1)−N(6)	103.8(3)	S(1)−Zn(1)−S(2)	112.28(9)
S(1)−Zn(1)−N(2)	112.6(2)	S(2)−Zn(1)−N(2)	108.5(2)
S(1)−Zn(1)−N(6)	107.1(2)	S(2)−Zn(1)−N(6)	112.4(2)

[a] Numbers in parentheses are estimated standard deviations.

Complexes Containing $(L2S)^-$. The complex [(L2S)ZnSPh], Figure 4B, shows a pseudotetrahedral coordination geometry about the Zn(II) ion where the two pyrazole nitrogens and one thiophenolate sulfur, from $(L2S)^-$, coordinate facially. This results in N(2)−Zn(1)−N(4) and average N_{pz}−Zn(1)−S(2) bond angles of 91.13(14) and 118.29(7)°, respectively, and Zn(1)−S(2) and average Zn(1)−N_{pz} bond distances of 2.246(1) and 2.041(3) Å. The exogenous "axial" thiolate S(1) is positioned nearly perpendicular to the trigonal plane formed by the pyrazolyl nitrogen and thiolate sulfur donor of $(L2S)^-$ with an Zn(1)−S(1) bond distance of 2.273(1) Å and average N_{pz}−Zn(1)−S(1) and S(2)−Zn(1)−S(1) bond angles of 100.54(7) and 122.16(5)°, respectively.

The molecular structure of $[(L2S)_2Zn]$ again confirms the near-tetrahedral coordination geometry around the Zn with two pyrazolyl nitrogens and two thiophenolate sulfurs from different molecules of $(L2S)^-$ coordinated to the Zn(II) ion, leaving one pyrazole nitrogen from each ligand uncoordinated. The thiophenolate sulfurs are positioned cis to one another with a S(1)−Zn(1)−S(2) bond angle of 112.28(9)° and an average Zn(1)−$S_{thiolate}$ bond distance of 2.291(1) Å. The pyrazolyl nitrogens are also cis with a N(2)−Zn(1)−N(6) bond angle of 103.8(3)° and an average Zn(1)−N_{pz} bond distance of 2.084(5) Å. In addition, the solid-state structure of $[(L2S)_2Zn]$ revealed two relatively short interactions between the metal ion and the hydrogen atoms connected to C(6) and C(28) with C(6)H···Zn(1) and C(28)H···Zn(1) distances of 3.137 and 3.093 Å, respectively.

Synthesis and Reactivity. Reaction of 1 equiv of the deprotonated ligand $L1O^-$ or $L2S^-$ with $ZnCl_2$ in acetonitrile produced the desired pseudotetrahedral LZnCl complexes. Other derivatives could be produced either by metathesis or reaction with silver salts of the desired ligand X to produce LZnX species. However in our hands the most useful synthon proved to be $LZnCH_3$ which was produced rapidly, in high yield and a high state of purity, from reaction of $Zn(CH_3)_2$ with either L1OH or L2SH in toluene. For $L1O^-$ reaction of the resulting methyl derivative with exogenous ligands, HX containing an acidic proton with a pK_a below ca. 9, proceeded with the evolution of methane and production of LZnX species. For ligands with pK_a values near this cutoff the success of the reaction appears to depend on the relative thiophilicity of Zn. Thus thiophenol or benzyl mercaptan cleanly produced the desired products within minutes while phenol itself did not react over a several day period.

Efforts to prepare LZnOH complexes by a variety of means with either $L1O^-$ or $L2S^-$ have thus far been unsuccessful. In the case of [(L1O)ZnCl], metathesis with KOH or (TBA)OH in a variety of solvents led only to demetalation and isolation of the free protonated ligand. Attempts to protonate $[(L1O)ZnCH_3]$ with water were also unsuccessful, as this complex was completely unreactive toward water. In contrast the thiophenolate complex, $[(L2S)ZnCH_3]$, was exceedingly reactive with water resulting in complete decomposition to products occurring within minutes to hours in solvents that were not rigorously dried. The final product of this reaction however was not the expected hydroxo complex but rather a tetrahedral N_2S_2 species $[(L2S)_2Zn]$ produced according to the following overall reaction:

$$2[(L2S)ZnCH_3] + 2H_2O \rightarrow 2CH_4\uparrow + Zn(OH)_2\downarrow + [(L2S)_2Zn] \quad (1)$$

Presumably the first step in the reaction sequence is protonation of the bound CH_3 and its loss as methane leaving [(L2S)ZnOH], indicating a much greater overall reactivity of $[(L2S)ZnCH_3]$ vs $[(L1O)ZnCH_3]$. However, [(L2S)ZnOH] appears to be unstable and quickly rearranges to $Zn(OH)_2$ and $[(L2S)_2Zn]$ driven both by the insolubility of the zinc hydroxide and the apparently enormous preference of Zn(II) to adopt a tetrahedral N_2S_2 geometry as recently pointed out by Vahrenkamp.[27] It is perhaps then not surprising that the N_2S_2 motif should have been used by nature as a very stable structural unit in the zinc finger proteins.

$[(L1OH)ZnI_2]$ can be prepared from the [(L1O)ZnI] complex by stoichiometric addition of HI (eq 2), resulting in protonation

$$[(L1O)ZnI] + HI \rightarrow [(L1OH)HZnI_2] \quad (2)$$

and loss of the phenolate arm from the coordination sphere and the addition of I^- in a crude approximation of the "tyrosine switch" mechanism.[1] It appears that the Zn−O_{phenol} bond is relatively weak and is easily removed by protonation. Attempts to prepare five coordinate Zn complexes of $L1O^-$ starting from $[(L1O)ZnCH_3]$ and bidentate HX reagents such as acetohydroxamic acid or hydroxyacetone met with failure. In the former case the phenolate arm was again protonated and the complex demetalated to produce free ligand and ZnX_2 while in the latter case it failed react at all.

The reaction of [(L1O)ZnSPh] and [(L1O)ZnSBz] with iodomethane in $CDCl_3$ or DMSO-d_6 yields the thioether and [(L1O)ZnI] as the alkylation products (eq 3).

$$[(L1O)ZnSR] + CH_3I \rightarrow [(L1O)ZnI] + CH_3SR \quad (3)$$

The thioether product is not coordinated to the Zn ion as determined by NMR. The reaction of [(L1O)ZnSBz] was >90% complete in less than 24 h, which is similar to the rate reported by Vahrenkamp for the corresponding tris(pyrazolyl)borate complex. The thiophenolate complex [(L1O)ZnSPh], however, reacted ca. 7× slower. The choice of solvent used did not materially affect the rate of either reaction. Attempts to follow the reaction of [(L2S)ZnSPh] with methyl iodide in either $CDCl_3$ or DMSO-d_6 by ^{1}H NMR spectroscopy were confounded by the formation of multiple products. Attempts to sort out this reaction are still in progress.

Discussion

Mixed nitrogen−thiolate coordination to Zn, once thought only to be found in structural sites such as "zinc finger" proteins and recently some prokaryotic metallothionines,[28] is now recognized as having a much wider role with an enzymatic function as well. Mixed N_2OS coordination for example is found in T7 lysozyme, bovine 5-aminolevulinate dehydratase, and peptide deformylase, where a pseudotetrahedral Zn is coordinated to two histidine nitrogens and a cysteinyl sulfur with water occupying the fourth position.[1] An NO_3S donor set characterizes farnesyl transferase,[29] and the NOS_2 coordination sphere is represented by cobalamin independent methionine synthase

(27) Burth, R.; Vahrenkamp, H. *Inorg. Chim. Acta* **1998**, *282*, 193.

(MetE)[30] and liver alcohol dehydrogenase.[1] While mixed N_2O coordination, where the oxygen donors come from aspartate or glutamate residues, are common in Zn metalloproteins, tyrosine phenolate oxygen donors are less so but are known to exist in the Zn endopeptidases, astacin and the serralysins.[1] Comparison between the Zn−donor atom bond lengths found in these complexes and various zinc metalloproteins reveals the expected similarities with a few exceptions. The average $Zn(1)-O_{Ph}$ distance for these complexes of 1.911(4) Å is considerably shorter than the $Zn-O_{Tyr}$ bond distances (∼3.0 Å) reported for *serratia* protease and alkaline protease.[31,32] However, the average $Zn-N_{pz}$ for the complexes containing $(L1O)^-$ is 2.06(2) Å and is only slightly shorter than the $Zn-N_{His}$ bond length of many zinc metalloproteins (∼2.1 Å).[1] The intermediate carboxylate coordination seen in the acetate moiety of [(L1O)ZnOAc] resembles that found in bacillolysin where the glutamate side chain coordinated to the zinc has $Zn-O_{Glu}$ bond distances of 2.1 and 2.5 Å, respectively.[33,34] The $Zn(1)-S_{thiolate}$ bond for all the complexes reported here are similar to those found in other small molecule zinc thiolate complexes [35,36] and slightly shorter (average $Zn(1)-S_{thiolate}$ bond length 2.264(1) Å) than those reported for Zn proteins such as cobalamin-dependent (MetH) and cobalamin-independent (MetE) methionine synthases with Zn−S bond distances of 2.32 and 2.31 Å, respectively.[30] Thus the L1OH and L2SH (N_2O and N_2S, respectively) family of ligands reported here are in principle excellent platforms with which to model the structure and reactivity of numerous Zn metalloproteins.

From a steric point of view ligands L1OH and L2SH most closely resemble the 3,5-dimethyltris(pyrazolyl)borates. While the *tert*-butyl group at the 3 position of the phenyl ring provides somewhat more side to side steric protection than does the single methyl on the analogous pyrazole of Tp^{Me2}, the Zn binding cavity is actually less deep. It is therefore somewhat remarkable that the coordinatively saturated L_2Zn "sandwich" complex is not observed in this study despite the fact that such a species is a thermodynamic sink with Tp^{Me2}.[24] Since such L_2M complexes *are* sterically capable of being formed with L1OH (we have isolated both the Co(II) and Ni(II) analogues)[21] the differences in chemistry among L1OH, L2SH, and Tp^{Me2} would appear to be based more on differing inherent reactivity rather than on steric bulk. Thus while reactions of $LZnCH_3$ species with HX yield only the ligand redistribution product, L_2Zn, with Tp^{Me2}, L1OH and L2OH react rapidly to give LZnX complexes.

In addition to their "normal" and expected roles as facially coordinating tridentate ligands, $(L1O)^-$ and $(L2S)^-$ display other coordination modes as well. In $[(L1OH)ZnI_2]$ the phenol arm is protonated and uncoordinated to the Zn, leaving L1OH to act as a simple N_2 bidentate ligand. Such a coordination mode has been observed in the analogous tris(pyrazolyl)borates.[37] Moresurprising was the coordination mode found in $[(L2S)_2Zn]$ where $(L2S)^-$ acts as an NS bidentate ligand with one of the pyrazole nitrogens remaining uncoordinated. Also unusual in this complex is the "inverted umbrella" configuration of the ligand (Figure 6), which, rather than having the three donor atoms directed away from the bridgehead carbon, has one of the pyrazole nitrogens and the thiolate sulfur pointed in. This conformation leads to, or perhaps is a result of, a moderate interaction between the Zn and hydrogens H6A and H28A connected to C(6) and C(28). Akita et al. have shown that the agostic interaction, B−H···Ru, in TpRu(H)(1,5-cyclooctadiene) complexes stabilizes the "inverted umbrella" isomer of the tris(pyrazolyl)borate ligand.[38] If these interactions can be viewed as bonding, then the Zn takes on a pseudooctahedral geometry and the large downfield shift of the methine bridgehead hydrogen from about 6.9 ppm in $[(L2S)ZnCH_3]$ to 10.3 ppm in $[(L2S)_2Zn]$ is indicative that the weak CH···Zn interaction persists in solution. Bouwman et. al. have recently reported an interaction between Ni(II) and an aromatic proton, which gives nearly identical "bond" lengths and NMR chemical shifts.[39] On the basis of the criteria described by Crabtree, however, both of these interactions are more attributable to hydrogen bonding than agostic interactions.[40]

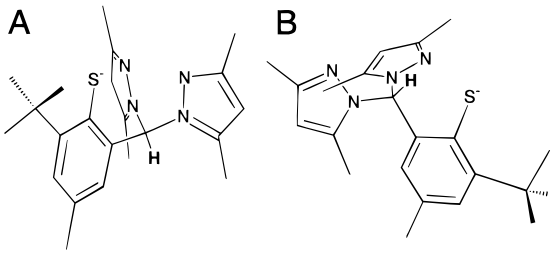

Figure 6. Facial (A) and inverted umbrella (B) configurations of $(L2S)^-$.

One of the fundamental questions that we hoped to address with this family of ligands is, given the similarities in the overall structures of Zn metalloproteins, how does the donor set modulate the reactivity of the pseudotetrahedral Zn(II) center. One aspect that is reproduced by the model complexes reported here is the relatively low affinity displayed by Zn for phenolate oxygen coordination. In Zn proteins with this coordination, it is manifested in long Zn−O phenolate bonds and in the tendency of the tyrosine to be displaced by incoming substrates and inhibitors, i.e. the tyrosine switch mechanism.[1] In the complexes of $(L1O)^-$, the $Zn-O_{phenolate}$ bond is not unusual, but attempts to react [(L1O)ZnX] with HX species often leads to protonation and loss of the phenolate group from the coordination sphere. Such chemistry is not observed for the thiol analogue $(L2S)^-$, where the thiolate sulfur always remains coordinated. Thus while Zn is usually classified as a "boarderline" hard metal, it displays a high degree of thiophilicity.

In an effort to mimic the activity toward alkyl group transfer from appropriate donors to coordinated cysteine residues of a number of zinc proteins including the *Escherichia coli* DNA repair protein, Ada, and the cobalamin dependent and independent methionine synthases, we have examined such reactions

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utilizing our model compounds. The role of the zinc ion in activating cysteine residues toward nucleophilic attack has been the subject of considerable recent activity.[41−44] In the most seminal model study to date, Wilker and Lippard have shown that, in reactions of $Zn(SPh)_4^{2-}$ and its derivatives with trimethyl phosphate as the methyl donor, the thiolate dissociates from the zinc prior to alkylation.[41] Another study by Darensbourg et al. using a solvated N_2S_2 tetradentate ligand complex of Zn and methyl iodide as the alkylating agent reached conclusions which were not inconsistent with this result.[42] More recently however evidence was presented by Vahrenkamp and co-workers for a nondissociative mechanism in the alkylation of TpZnSR complexes by a variety of methylating agents.[43] We have examined the methyl transfer reaction between methyl iodide or trimethyl phosphate and the complexes [(L1O)ZnSPh], [Zn(L1O)SBz], and [(L2S)ZnSPh] in both polar (DMSO) and nonpolar ($CHCl_3$) solvents. In either solvent there was no detectable reaction with any of the complexes even after several weeks using the weak methyl donor, trimethyl phosphate, while methyl iodide reacted with all three complexes at varying rates which were independent of solvent. Our results with methyl iodide are in accord with those of Vahrenkamp et al.[43] The lack of an appreciable solvent dependence and the fact that the benzyl mercaptan derivative reacted much faster than the thiophenol, despite its significantly greater pK_a, are not consistent with free thiolate being the reactive species in a dissociative mechanism. They do however support the intermolecular four-center Zn−S/C−X transition state proposed by Vahrenkamp. At the same time the sharp NMR spectra of our complexes even in DMSO, indicative of little or no thiolate dissociation, is consistent with a lack of any reactivity toward trimethyl phosphate. Thus it appears that there may be several mechanisms by which Zn complexes can modulate the reactivity of cysteine thiolates; i.e., they can control the amount of "free" thiolate (a very powerful nucleophile) as in the reaction of $Zn(SPh)_4^{2-}$ with trimethyl phosphate and by analogy the Ada protein and methylated DNA or they can direct reaction of methyl donors toward coordinated cysteines via an intermolecular transition state.

One final point: In none of the model reactions studied to date, including our own, has the thioether resulting from the methylation remained in the metal coordination sphere. Vahrenkamp has proposed that the poor donor ability of thioethers toward Zn(II) might be part of the driving force for these reactions. However, it should be noted that in the Ada protein, at least, the methylated cysteine *is* coordinated to the zinc and there is at least one clear-cut example in the inorganic literature of a Zn-coordinated thioether.[14] Thus it remains unclear under which conditions a thioether may be a Zn ligand.

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Supporting Information Available: Complete listings of atomic positions, bond lengths and angles, anisotropic thermal parameters, hydrogen atom coordinates, and data collection and crystal parameters and ORTEP diagrams for all crystallographically characterized complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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